WEST Search History

DATE: Monday, October 27, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L7	L2 not l5	45	L7
L6	L5 and (nutral or alkaline)	67	L6
L5	L2 and (gene or nucleic acid or clon? or dna or cdna)	151	L5
L4	ceramidase same (mice or mouse)	16	L4
L3	L2 and (mice or mouse)	116	L3
L2	ceramidase	196	L2
DB=USPT; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L1	('6258581')[PN]	1	L1

END OF SEARCH HISTORY

```
=> file reg
=> s ceramide/cn
L1            1 CERAMIDE/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   104404-17-3  REGISTRY
CN   Ceramide (9CI)  (CA INDEX NAME)
MF   Unspecified
CI   COM, MAN
SR   CA
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CAPLUS,
       CBNB, CIN, CSCHEM, NAPRALERT, PIRA, PROMT, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE
               8 REFERENCES IN FILE CA (1907 TO DATE)
               2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
               8 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> s C12-nbd-ceramide/cn
L2            0 C12-NBD-CERAMIDE/CN

=> s nbd-ceramide/cn
L3            0 NBD-CERAMIDE/CN

=> file .nash
=> s ceramidase
L4          266 FILE MEDLINE
L5          294 FILE CAPLUS
L6          247 FILE SCISEARCH
L7           55 FILE LIFESCI
L8          311 FILE BIOSIS
L9          198 FILE EMBASE

TOTAL FOR ALL FILES
L10        1371 CERAMIDASE

=> s ceramidase  and (nucleic acid or cdna or dna or gene)


TOTAL FOR ALL FILES
L17         406 CERAMIDASE AND (NUCLEIC ACID OR CDNA OR DNA OR GENE)

=> s l17 not 2000-2003/py
TOTAL FOR ALL FILES
L24         141 L17 NOT 2000-2003/PY

=> dup rem l24
PROCESSING COMPLETED FOR L24
L25           46 DUP REM L24 (95 DUPLICATES REMOVED)

=> d ibib abs 1-46

L25  ANSWER 1 OF 46  CAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:         2000:751594  CAPLUS
DOCUMENT NUMBER:          133:330167
TITLE:                    Cloning and characterization of the human and murine
                          acid ceramidase cDNAs and
                          genes, and generation of acid
                          ceramidase deficient mice by gene
                          targeting
AUTHOR(S):                Li, Chi-Ming
CORPORATE SOURCE:         Mount Sinai Sch. Med. New York Univ., USA
SOURCE:                   (1999) 171 pp.  Avail.: UMI, Order No. DA9961716
                          From: Diss. Abstr. Int., B 2000, 61(2), 664
DOCUMENT TYPE:            Dissertation
LANGUAGE:                 English
```

AB Unavailable

L25 ANSWER 2 OF 46 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2000062886 MEDLINE
DOCUMENT NUMBER: 20062886 PubMed ID: 10593963
TITLE: Molecular cloning, sequencing, and expression of the **gene** encoding alkaline **ceramidase** from Pseudomonas aeruginosa. Cloning of a **ceramidase** homologue from Mycobacterium tuberculosis.
AUTHOR: Okino N; Ichinose S; Omori A; Imayama S; Nakamura T; Ito M
CORPORATE SOURCE: Department of Bioscience and Biotechnology, Division of Bioresource and Bioenvironmental Sciences, Graduate School Kyushu University, Hakozaki 6-10-1, Higashi-ku, Fukuoka 812-8581, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Dec 17) 274 (51) 36616-22.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB028646
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

AB We previously reported the purification and characterization of a novel type of alkaline **ceramidase** from Pseudomonas aeruginosa strain AN17 (Okino, N., Tani, M., Imayama, S., and Ito, M. (1998) J. Biol. Chem. 273, 14368-14373). Here, we report the molecular cloning, sequencing, and expression of the **gene** encoding the **ceramidase** of this strain. Specific oligonucleotide primers were synthesized using the peptide sequences of the purified **ceramidase** obtained by digestion with lysylendopeptidase and used for polymerase chain reaction. **DNA** fragments thus amplified were used as probes to clone the **gene** encoding the **ceramidase** from a genomic library of strain AN17. The open reading frame of 2,010 nucleotides encoded a polypeptide of 670 amino acids including a signal sequence of 24 residues, 64 residues of which matched the amino acid sequence determined for the purified enzyme. The molecular weight of the mature enzyme was estimated to be 70,767 from the deduced amino acid sequence. Expression of the **ceramidase gene** in Escherichia coli, resulted in production of a soluble enzyme with the identical N-terminal amino acid sequence. Recombinant **ceramidase** was purified to homogeneity from the lysate of E. coli cells and confirmed to be identical to the Pseudomonas enzyme in its specificity and other enzymatic properties. No significant sequence similarities were found in other known functional proteins including human acid **ceramidase**. However, we found a sequence homologous to the **ceramidase** in hypothetical proteins encoded in Mycobacterium tuberculosis, Dictyostelium discoideum, and Arabidopsis thaliana. The homologue of the **ceramidase gene** was thus cloned from an M. tuberculosis cosmid and expressed in E. coli, and the **gene** was demonstrated to encode an alkaline **ceramidase**. This is the first report for the cloning of an alkaline **ceramidase**.

L25 ANSWER 3 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2000036602 MEDLINE
DOCUMENT NUMBER: 20036602 PubMed ID: 10567432
TITLE: Activation of sphingosine kinase by tumor necrosis factor-alpha inhibits apoptosis in human endothelial cells.
AUTHOR: Xia P; Wang L; Gamble J R; Vadas M A
CORPORATE SOURCE: Division of Human Immunology, The Hanson Centre for Cancer Research, Adelaide, South Australia 5000, Australia.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Nov 26) 274 (48) 34499-505.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991229

AB Human umbilical vein endothelial cells (HUVEC), like most normal cells, are resistant to tumor necrosis factor-alpha (TNF)-induced apoptosis in spite of TNF activating sphingomyelinase and generating ceramide, a known inducer of apoptosis. Here we report that TNF activates another key enzyme, sphingosine kinase (SphK), in the sphingomyelin metabolic pathway resulting in production of sphingosine-1-phosphate (S1P) and that S1P is a potent antagonist of TNF-mediated apoptosis. The TNF-induced SphK activation is independent of sphingomyelinase and **ceramidase** activities, suggesting that TNF affects this enzyme directly other than through a mass effect on sphingomyelin degradation. In contrast to normal HUVEC, in a spontaneously transformed endothelial cell line (C11) TNF stimulation failed to activate SphK and induced apoptosis as characterized by morphological and biochemical criteria. Addition of exogenous S1P or increasing endogenous S1P by phorbol ester markedly protected C11 cell line from TNF-induced apoptosis. Conversely, N, N-dimethylsphingosine, an inhibitor of SphK, profoundly sensitized normal HUVEC to killing by TNF. Thus, we demonstrate that the activation of SphK by TNF is an important signaling for protection from the apoptotic effect of TNF in endothelial cells.

L25 ANSWER 4 OF 46 EMBASE
on STN

ACCESSION NUMBER: 1999268925 EMBASE
TITLE: Role of sphingosine 1-phosphate in the mitogenesis induced by oxidized low density lipoprotein in smooth muscle cells via activation of sphingomyelinase, **ceramidase**, and sphingosine kinase.
AUTHOR: Auge N.; Nikolova-Karakashian M.; Carpentier S.; Parthasarathy S.; Negre- Salvayre A.; Salvayre R.; Merrill A.H. Jr.; Levade T.
CORPORATE SOURCE: T. Levade, INSERM U. 466, Laboratoire de Biochimie, Institut Louis Bugnard, 1 Avenue Jean Poulhes, F-31403 Toulouse Cedex 4, France. levade@rangueil.inserm.fr
SOURCE: Journal of Biological Chemistry, (30 Jul 1999) 274/31 (21533-21538).
Refs: 54
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Oxidized LDL (oxLDL) have been implicated in diverse biological events leading to the development of atherosclerotic lesions. We previously demonstrated that the proliferation of cultured vascular smooth muscle cells (SMC) induced by oxLDL is preceded by an increase in neutral sphingomyelinase activity, sphingomyelin turnover to ceramide, and stimulation of mitogen- activated protein kinases (Auge, N., EscargueilBlanc, I., Lajoie-Mazenc, I., Suc, I., Andrieu-Abadie, N., Pieraggi, M. T., Chatelut, M., Thiers, J. C., Jaffrezou, J. P., Laurent, G., Levade, T., Negre-Salvayre, A., and S alvayre, R. (1998) J. Biol. Chem. 273, 12893-12900). Since ceramide can be converted to other bioactive metabolites, such as the well established mitogen sphingosine 1-phosphate (S1P), we investigated whether additional ceramide metabolites are involved in the oxLDLinduced SMC proliferation. We report here that incubation of SMC with oxLDL increased the activities of both acidic and alkaline **ceramidases** as well as sphingosine kinasem and elevated cellular sphingosine and S1P. Furthermore the mitogenic effect of oxLDL was inhibited by D-erythro-2-(N-myristoylamino)-1-phenyl-1propanol and N,N- dimethylsphingosine which are in- hibitors of **ceramidase** and sphingosine kinase, respectively. These findings suggest that S1P is a key mediator oltre mitogenic effect of oxLDL. In agreement with this conclusion, exogenous addition of sphingosine stimulated the proliferation of cultured SMC, and this effect was abrogated by dimethylsphingosine but not by fumonisin B1, an inhibitor of the acylation of sphingosine to ceramide. Exogenous S1P also promoted SMC proliferation. Altogether, these results Strongly suggest that the mitogenic effect of oxLDL in SMC

involves the combined activation of sphingomyelinase(s), **ceramidase**(s), and sphingosine kinase, resulting in the turnover of sphingomyelin to a number of sphingolipid metabolites, of which at least SiP is critical for mitogenesis.

L25 ANSWER 5 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE 2
ACCESSION NUMBER: 1999:357325 SCISEARCH
THE GENUINE ARTICLE: 192BC
TITLE: A novel pathway for tumor necrosis factor-alpha and ceramide signaling involving sequential activation of tyrosine kinase, p21(ras), and phosphatidylinositol 3-kinase
AUTHOR: Hanna A N; Chan E Y W; Xu J; Stone J C; Brindley D N (Reprint)
CORPORATE SOURCE: UNIV ALBERTA, SIGNAL TRANSDUCT LABS, LIPID & LIPOPROT RES GRP, HERITAGE MED RES CTR 357, EDMONTON, AB T6G 2S2, CANADA (Reprint); UNIV ALBERTA, SIGNAL TRANSDUCT LABS, LIPID & LIPOPROT RES GRP, HERITAGE MED RES CTR 357, EDMONTON, AB T6G 2S2, CANADA; UNIV ALBERTA, DEPT BIOCHEM, EDMONTON, AB T6G 2S2, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (30 APR 1999) Vol. 274, No. 18, pp. 12722-12729.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 67

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Treatment of confluent rata fibroblasts with C-2-ceramide (N-acetylsphingosine), sphingomyelinase, or tumor necrosis factor-alpha (TNF alpha) increased phosphatidylinositol (PI) 3-kinase activity by 3-6-fold after 10 min. This effect of C-2-ceramide depended on tyrosine kinase activity and an increase in Ras-GTP levels. Increased PI 3-kinase activity was also accompanied by its translocation to the membrane fraction, increases in tyrosine phosphorylation of the p85 subunit, and physical association with Pas, Activation of PI 3-kinase by TNF alpha, sphingomyelinase, and C-2-ceramide was inhibited by tyrosine kinase inhibitors (genistein and PP1). The stimulation of PI S-kinase by sphingomyelinase and C-2-ceramide was not observed in fibroblasts expressing dominant-negative Pas (N17) and the stimulation by TNF alpha was decreased by 70%. PI 3-kinase activation by C-2-ceramide was not modified by inhibitors of acidic and neutral **ceramidases**, and it was not observed with the relatively inactive analog, dihydro-C-2-ceramide It is proposed that activation of Pas and PI 3-kinase by ceramide can contribute to signaling effects of TNF alpha that occur downstream of sphingomyelinase activation and result in increased fibroblasts proliferation.

L25 ANSWER 6 OF 46 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 1999167483 MEDLINE
DOCUMENT NUMBER: 99167483 PubMed ID: 10066779
TITLE: Nitric oxide donors induce stress signaling via ceramide formation in rat renal mesangial cells.
AUTHOR: Huwiler A; Pfeilschifter J; van den Bosch H
CORPORATE SOURCE: Center for Biomembranes and Lipid Enzymology, University of Utrecht, Padualaan 8, 3584 CH Utrecht, The Netherlands.. huwiler@em.uni-frankfurt.de
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Mar 12) 274 (11) 7190-5.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413

AB Exogenous NO is able to trigger apoptosis of renal mesangial cells, and thus may contribute to acute lytic phases as well as to resolution of glomerulonephritis. However, the mechanism involved in these events is still unclear. We report here that chronic exposure of renal mesangial cells for 24 h to compounds releasing NO, including spermine-NO, (Z)-1-N-methyl-N-[6-(N-methylammoniohexyl)amino] diazen-1-+ ++ium-1, 2-diolate (MAHMA-NO), S-nitrosoglutathione (GS-NO), and S-nitroso-N-acetyl-D,L-penicillamine (SNAP) results in a potent and dose-dependent increase in the lipid signaling molecule ceramide. Time courses reveal that significant effects occur after 2-4 h of stimulation with NO donors and reach maximal levels after 24 h of stimulation. No acute (within minutes) ceramide production can be detected. When cells were stimulated with NO donors in the presence of phorbol ester, a direct activator of protein kinase C, both ceramide production and **DNA** fragmentation are completely abolished. Furthermore, addition of exogenous ceramide partially reversed the inhibitory effect of phorbol ester on apoptosis, thus suggesting a negative regulation of protein kinase C on ceramide formation and apoptosis. In contrast to exogenous NO, tumor necrosis factor (TNF)-alpha stimulates a very rapid and transient increase in ceramide levels within minutes but fails to induce the late-phase ceramide formation. Moreover, TNF fails to induce apoptosis in mesangial cells. Interestingly, NO and TNFalpha cause a chronic activation of acidic and neutral sphingomyelinases, the ceramide-generating enzymes, whereas acidic and neutral **ceramidases**, the ceramide-metabolizing enzymes, are inhibited by NO, but potently stimulated by TNFalpha. Furthermore, in the presence of an acidic **ceramidase** inhibitor, N-oleoylethanolamine, TNFalpha leads to a sustained accumulation of ceramide and in parallel induces **DNA** fragmentation. In summary, our data demonstrate that exogenous NO causes a chronic up-regulation of ceramide levels in mesangial cells by activating sphingomyelinases and concomitantly inhibiting **ceramidases**, and that particularly the late-phase of ceramide generation may be responsible for the further processing of a proapoptotic signal.

L25 ANSWER 7 OF 46 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999291785 MEDLINE
DOCUMENT NUMBER: 99291785 PubMed ID: 10365663
TITLE: Retrovirus-mediated correction of the metabolic defect in cultured Farber disease cells.
AUTHOR: Medin J A; Takenaka T; Carpentier S; Garcia V; Basile J P; Segui B; Andrieu-Abadie N; Auge N; Salvayre R; Levade T
CORPORATE SOURCE: Department of Medicine, University of Illinois at Chicago, 60607-7173, USA.. jmedin@uic.edu
SOURCE: HUMAN GENE THERAPY, (1999 May 20) 10 (8) 1321-9.
Journal code: 9008950. ISSN: 1043-0342.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 20000229
Entered Medline: 19990824

AB Farber disease is a rare severe lysosomal storage disorder due to a deficient activity of the enzyme acid **ceramidase** (AC). Patients have granulomas along with lipid-laden macrophages that accumulate in a number of tissues, leading to multiple diverse clinical symptoms. There is no therapy for the disorder and most patients succumb to the disease in early childhood. The severity of the disease progression seems to correlate with the amount of the accumulated ceramide substrate. Since the **cDNA** for human AC has been elucidated we sought to establish if genetic transfer of this sequence would lead to enzymatic and, especially, functional correction of the catabolic defect in Farber patient cells. To do this, a novel amphotropic recombinant retrovirus was constructed that engineers transfer of the human AC **cDNA**. On infection of patient fibroblasts, AC enzyme activity in cell extracts was completely restored. Further, substrate-loading assays of intact living cells showed a fully normalized catabolism of lysosomal ceramide. Lastly, as reported for some other corrected enzymatic defects of lysosomes, metabolic cooperativity was seen, in that functionally corrected patient fibroblasts secreted AC that was taken up through the mannose 6-phosphate

receptor and used by uncorrected fibroblasts as well as recipient Farber lymphoblastoid cells. This overall transduction and uptake scenario for Farber disease allows future treatment of this severe disorder to be envisioned using **gene** transfer approaches.

L25 ANSWER 8 OF 46 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999258771 MEDLINE
DOCUMENT NUMBER: 99258771 PubMed ID: 10328219
TITLE: Rapid screening of specific changes in mRNA in thyroid carcinomas by sequence specific-differential display: decreased expression of acid **ceramidase** mRNA in malignant and benign thyroid tumors.
AUTHOR: Maeda I; Takano T; Matsuzuka F; Maruyama T; Higashiyama T; Liu G; Kuma K; Amino N
CORPORATE SOURCE: Central Laboratory for Clinical Investigation, Osaka University Hospital, Suita, Japan.. maeda@hp-lab.med.osaka-u.ac.jp
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1999 May 31) 81 (5) 700-4.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990714
Last Updated on STN: 20000229
Entered Medline: 19990625
AB Sequence specific-differential display (SS-DD) is a powerful method for screening significant changes in **gene** expression between normal and malignant tissues. Using this method, we detected 3 **genes** for which the expression is much decreased in thyroid tumors. After sub-cloning and sequencing analysis, one of the **genes** was revealed to be acid **ceramidase** (AC). The expression of AC in normal thyroids and thyroid tumors was examined by semi-quantitative reverse-transcription-polymerase-chain-reaction (RT-PCR). Obvious decreases in the expression of AC mRNA were observed in 5/6 follicular adenomas, 2/2 adenomatous goiters, 3/6 papillary carcinomas and 1/2 follicular carcinomas. To confirm this result, real-time quantitative PCR analysis (TaqMan PCR) was carried out. The relative expression level of AC mRNA compared with that of GAPDH mRNA was reduced in follicular adenomas, follicular carcinomas, and papillary carcinomas. Further, the expression of AC mRNA was extremely reduced in 2 anaplastic carcinomas. These results suggest a possible relationship between thyroid tumorigenesis and the expression of AC mRNA. Moreover, the increased expression of AC mRNA in normal thyroid tissues suggests some fundamental roles of AC in thyroid function.

L25 ANSWER 9 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE 6
ACCESSION NUMBER: 1999:456407 SCISEARCH
THE GENUINE ARTICLE: 204EL
TITLE: Ceramide accumulation is associated with increased apoptotic cell death in cultured fibroblasts of sphingolipid activator protein-deficient mouse but not in fibroblasts of patients with Farber disease
AUTHOR: Tohyama J; Oya Y; Ezoe T; Vanier M T; Nakayasu H; Fujita N; Suzuki K (Reprint)
CORPORATE SOURCE: UNIV N CAROLINA, SCH MED, CTR NEUROSCI, CB 7250, CHAPEL HILL, NC 27599 (Reprint); UNIV N CAROLINA, SCH MED, CTR NEUROSCI, CHAPEL HILL, NC 27599; UNIV N CAROLINA, DEPT PATHOL & LAB MED, CHAPEL HILL, NC 27599; UNIV N CAROLINA, DEPT NEUROL, CHAPEL HILL, NC 27599; UNIV N CAROLINA, DEPT PSYCHIAT, CHAPEL HILL, NC 27599; CTR HOSP LYON SUD, LYON SUD SCH MED, OULLINS, FRANCE; CTR HOSP LYON SUD, FDN GILLET MERIEUX, OULLINS, FRANCE
COUNTRY OF AUTHOR: USA; FRANCE
SOURCE: JOURNAL OF INHERITED METABOLIC DISEASE, (JUN 1999) Vol. 22, No. 5, pp. 649-662.
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS.
ISSN: 0141-8955.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 49
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Ceramide is recognized as an intracellular mediator of cell growth, differentiation and apoptosis. Tumour necrosis factor, anti-fas antibody, radiation and anticancer drugs such as actinomycin D are known to induce apoptosis in several cell types through generation of ceramide by activation of the sphingomyelinase pathway or ceramide synthetase. In this study, we examined the occurrence of apoptosis in fibroblasts from patients with Farber disease and from sphingolipid activator protein-deficient (sap -/-) mouse. These cells accumulate ceramide as the result of genetic deficiency of acid **ceramidase** and the **ceramidase** activator (sap-D), respectively. Amounts of ceramide in fibroblasts from Farber patients and in fibroblasts from sap -/- mouse were increased 2.9-fold and 2.8-fold, respectively, over the level of controls. Despite the similar degree of ceramide accumulation, cells exhibiting apoptotic features were increased only in fibroblasts from the sap -/- mouse but not those from the Farber patients. Thymidine uptake of Farber fibroblasts was normal while that of sap -/- mouse fibroblasts was twice normal, consistent with the apparently normal growth and the different rates of apoptotic cell death in these two cell lines. These data suggest that intralysosomal accumulation of ceramide due to defective acid **ceramidase** or its activator may not play an important role as a mediator of apoptosis. The increased apoptosis in the cultured fibroblasts from the sap -/- mouse may be caused by mechanisms other than the ceramide accumulation. Although more frequent than normal, significant apoptotic cell death was not observed in sap -/- mouse brain in vivo.

L25 ANSWER 10 OF 46 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000189953 MEDLINE
DOCUMENT NUMBER: 20189953 PubMed ID: 10723061
TITLE: Differential responses of oligodendrocytes to tumor necrosis factor and other pro-apoptotic agents: role of ceramide in apoptosis.
AUTHOR: Scurlock B; Dawson G
CORPORATE SOURCE: Committee on Neurobiology, Department of Pediatrics, University of Chicago, Chicago, Illinois 60637, USA.
CONTRACT NUMBER: NS-36866 (NINDS)
SOURCE: JOURNAL OF NEUROSCIENCE RESEARCH, (1999 Feb 15) 55 (4) 514-22.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000407
Last Updated on STN: 20000407
Entered Medline: 20000329

AB Staurosporine induced apoptosis in a human oligodendroglioma cell line (HOG), neonatal rat oligodendrocyte (O2A(+)) precursors, and mature rat oligodendrocytes. In all three cell culture systems, the activation of caspase-3-like activity (CPP32) coincided with the increased formation of ceramide from sphingomyelin and the onset of **DNA** fragmentation. Further, the addition of exogenous C(2)-ceramide induced CPP32 activation and **DNA** fragmentation in all three culture systems. Raising endogenous ceramide levels by the addition of the **ceramidase** inhibitor, oleoylethanolamine, enhanced apoptosis in both a time- and concentration-dependent manner. Inhibitors of phosphatidylinositol 3-kinase (wortmannin and LY294002) also induced caspase-3 (CPP32) activation, increased ceramide formation, induced **DNA** fragmentation, and reduced cell viability. In contrast, cytokines such as tumor necrosis factor-alpha (TNF-alpha) had a differential effect on the three cell cultures. Thus, TNF-alpha (160 ng/ml) induced 70% apoptosis in 24 hr in freshly isolated rat brain O2A(+) precursor cells, 60% apoptosis in 24 hr in a human oligodendroglioma (HOG) cell line, but no apoptosis in mature neonatal rat oligodendrocytes. Interferon-gamma augmented the activation of CPP32 by TNF-alpha in HOG cells and O2A(+) oligodendrocyte precursor cells but had no effect on mature oligodendrocytes. Thus, the

death pathway appears to be similar in the three cell lines but the lack of coupling between TNF-alpha receptors and the apoptotic pathway leads to a lack of response to cytokines in mature oligodendrocytes.

L25 ANSWER 11 OF 46 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999355000 MEDLINE
DOCUMENT NUMBER: 99355000 PubMed ID: 10428046
TITLE: Induction of the manganese superoxide dismutase **gene** by sphingomyelinase and ceramide.
AUTHOR: Pahan K; Dobashi K; Ghosh B; Singh I
CORPORATE SOURCE: Department of Pediatrics, Medical University of South Carolina, Charleston 29425, USA.
CONTRACT NUMBER: NS-22576 (NINDS)
NS-34741 (NINDS)
NS-37766 (NINDS)
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1999 Aug) 73 (2) 513-20.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990813

AB The present study reports the effect of ceramide generated by hydrolysis of membrane sphingomyelin with bacterial sphingomyelinase (SMase) and of cell-permeable ceramide analogues on the expression of manganese superoxide dismutase (MnSOD). Incubation of the rat primary astrocytes with SMase led to a time- and dose-dependent increase in MnSOD activity. The increase in MnSOD activity was accompanied by an increase in MnSOD protein and mRNA. A similar effect on the expression of MnSOD was observed with the addition of cell-permeable ceramide analogues (C2 and C6). On the other hand, C2-dihydroceramide (N-acetylsphinganine), which lacks the functional critical double bond, was ineffective in inducing the expression of MnSOD. Nuclear run-on analysis showed that SMase and ceramide increased the rate of transcription of the MnSOD **gene**. Besides astrocytes, SMase was also found to induce the expression of MnSOD in rat mesangial cells, C6 glial cells, PC12 cells, and human skin fibroblasts. Markedly higher expression of mRNA, protein, and activity of MnSOD in skin fibroblasts from patients with Farber disease, a human disorder with pathognomonic accumulation of ceramide due to a deficiency of **ceramidase**, than in normal skin fibroblasts indicate that ceramide may act as a physiological inducer of MnSOD **gene** expression. However, stimulation of ceramide-mediated **DNA** fragmentation by antisense knockdown of MnSOD suggests that induction of MnSOD by ceramide is a protective response of the cell.

L25 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:601017 CAPLUS
DOCUMENT NUMBER: 131:284219
TITLE: Sphingomyelin hydrolysis and regulation of the expression of the **gene** for cytochrome P450
AUTHOR(S): Merrill, A. H., Jr.; Morgan, E. T.; Nikolova-Karakashian, M.; Stewart, J.
CORPORATE SOURCE: Department of Biochemistry, 4113 Rollins Research Center, Emory University School of Medicine, Atlanta, GA, 30322-3050, USA
SOURCE: Biochemical Society Transactions (1999), 27(4), 383-387
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 32 refs. on the effect of sphingolipids on the expression of cytochrome P 450 isoforms; interleukin 1.beta. (IL-1.beta.) stimulated hydrolysis of sphingomyelin to ceramide, the induction of .alpha.1-acid glycoprotein expression by exogenous sphingolipids, and CYP2C11 suppression by sphingosine and ceramides in rat hepatocytes; activation of **ceramidases** by IL-1.beta..

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 13 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:525174 BIOSIS
DOCUMENT NUMBER: PREV199900525174
TITLE: Human acid **ceramidase** located at 8p22 is overexpressed but not mutated in prostate cancer.
AUTHOR(S): Seelan, R. S. [Reprint author]; Qian, C. [Reprint author]; Yokomizo, A. [Reprint author]; Smith, D. I. [Reprint author]; Liu, W. [Reprint author]
CORPORATE SOURCE: Div. of Experimental Pathology, Mayo Clinic and Foundation, Rochester, MN, USA
SOURCE: American Journal of Human Genetics, (Oct., 1999) Vol. 65, No. 4, pp. A321. print.
Meeting Info.: 49th Annual Meeting of the American Society of Human Genetics. San Francisco, California, USA. October 19-23, 1999. The American Society of Human Genetics.
CODEN: AJHGAG. ISSN: 0002-9297.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 1999
Last Updated on STN: 3 Dec 1999

L25 ANSWER 14 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE 9
ACCESSION NUMBER: 1999:521782 SCISEARCH
THE GENUINE ARTICLE: 210YF
TITLE: Epidermal growth factor inhibits ceramide-induced apoptosis and lowers ceramide levels in primary placental trophoblasts
AUTHOR: Payne S G; Brindley D N; Guilbert L J (Reprint)
CORPORATE SOURCE: UNIV ALBERTA, DEPT MED MICROBIOL & IMMUNOL, PERINATAL RES CTR, 625 HMRC, EDMONTON, AB T6G 2S2, CANADA (Reprint); UNIV ALBERTA, DEPT MED MICROBIOL & IMMUNOL, PERINATAL RES CTR, EDMONTON, AB T6G 2S2, CANADA; UNIV ALBERTA, DEPT BIOCHEM, SIGNAL TRANSDUCT LABS, EDMONTON, AB, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (AUG 1999) Vol. 180, No. 2, pp. 263-270.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0021-9541.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 59
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The activation of sphingomyelinase and the subsequent generation of ceramide are emerging as important components of signaling pathways leading to apoptosis. The combination of tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) induces apoptosis of primary placental trophoblasts in vitro. This apoptosis is inhibited completely by cotreatment with epidermal growth factor (EGF). We therefore examined the role of sphingomyelinase and ceramide in trophoblast apoptosis and how this may be influenced by EGF. Exogenous C-16-ceramide (20 mu M) and acid sphingomyelinase induced trophoblast apoptosis, an effect abrogated completely by cotreatment with 10 ng/ml EGF. Neutral sphingomyelinase also increased ceramide levels but did not induce apoptosis. Treatment with EGF alone decreased cellular ceramide levels. This decrease could be blocked by cotreatment with the acid **ceramidase** inhibitor N-oleoylethanolamine (OE). OE alone increased ceramide levels and induced apoptosis that could not be blocked by cotreatment with EGF. In contrast, the alkaline **ceramidase** inhibitor D-MAPP, although it also increased ceramide levels, did not induce apoptosis nor did it affect TNF-alpha/IFN-alpha-induced cell death. These results implicate sphingolipids as important mediators in trophoblast apoptosis and suggest that the antiapoptotic properties of EGF can in part be explained by its control of ceramide concentrations in trophoblasts. (C) 1999 Wiley-Liss, Inc.

L25 ANSWER 15 OF 46 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000079156 MEDLINE
DOCUMENT NUMBER: 20079156 PubMed ID: 10610717
TITLE: Molecular cloning and characterization of a human **cDNA** and **gene** encoding a novel acid **ceramidase**-like protein.
AUTHOR: Hong S B; Li C M; Rhee H J; Park J H; He X; Levy B; Yoo O J; Schuchman E H
CORPORATE SOURCE: Department of Human Genetics, Mount Sinai School of Medicine, New York 10029, USA.
CONTRACT NUMBER: DK 54830 (NIDDK)
HD 28607 (NICHD)
SOURCE: GENOMICS, (1999 Dec 1) 62 (2) 232-41.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000209

AB Computer-assisted database analysis of sequences homologous to human acid **ceramidase** (ASAH) revealed a 1233-bp **cDNA** (previously designated cPj-LTR) whose 266-amino-acid open reading frame had approximately 36% identity with the ASAH polypeptide. Based on this high degree of homology, we undertook further molecular characterization of cPj-LTR and now report the full-length **cDNA** sequence, complete **gene** structure (renamed human ASAHL since it is a human acid **ceramidase**-like sequence), chromosomal location, primer extension and promoter analysis, and transient expression results. The full-length human ASAHL **cDNA** was 1825 bp and contained an open-reading frame encoding a 359-amino-acid polypeptide that was 33% identical and 69% similar to the ASAH polypeptide over its entire length. Numerous short regions of complete identity were observed between these two sequences and two sequences obtained from the Caenorhabditis elegans genome database. The 30-kb human ASAHL genomic sequence contained 11 exons, which ranged in size from 26 to 671 bp, and 10 introns, which ranged from 150 bp to 6.4 kb. The **gene** was localized to the chromosomal region 4q21.1 by fluorescence in situ hybridization analysis. Northern blotting experiments revealed a major 2.0-kb ASAHL transcript that was expressed at high levels in the liver and kidney, but at relatively low levels in other tissues such as the lung, heart, and brain. Sequence analysis of the 5'-flanking region of the human ASAHL **gene** revealed a putative promoter region that lacked a TATA box and was GC rich, typical features of a housekeeping **gene** promoter, as well as several tissue-specific and/or hormone-induced transcription regulatory sites. 5'-Deletion analysis localized the promoter activity to a 1. 1-kb fragment within this region. A major transcription start site also was located 72 bp upstream from the ATG translation initiation site by primer extension analysis. Expression analysis of a green fluorescence protein/ASAHL fusion protein in COS-1 cells revealed a punctate, perinuclear distribution, although no acid **ceramidase** activity was detected in the transfected cells using a fluorescence-based in vitro assay system.

L25 ANSWER 16 OF 46 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2000079155 MEDLINE
DOCUMENT NUMBER: 20079155 PubMed ID: 10610716
TITLE: The human acid **ceramidase gene** (ASAH): structure, chromosomal location, mutation analysis, and expression.
AUTHOR: Li C M; Park J H; He X; Levy B; Chen F; Arai K; Adler D A; Disteche C M; Koch J; Sandhoff K; Schuchman E H
CORPORATE SOURCE: Department of Human Genetics, Mount Sinai School of Medicine, New York 10029, USA.
CONTRACT NUMBER: DK 54830 (NIDDK)
HD 28607 (NICHD)
RR 0071 (NCRR)
SOURCE: GENOMICS, (1999 Dec 1) 62 (2) 223-31.

Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20010815
Entered Medline: 20000209

AB Acid **ceramidase** (AC) is the lysosomal enzyme that degrades ceramide into sphingosine and fatty acid. A deficiency in human AC activity leads to the lysosomal storage disorder, Farber disease (FD). The human AC **gene** (HGMW-approved symbol ASAH) was cloned and characterized, revealing an organization similar to that of the murine AC **gene**. The human **gene** spans about 30 kb in length and contains 14 exons ranging in size from 46 to 1201 bp. The exon/intron junctions were determined and found to follow the GT-AG rule. The putative promoter region had a GC content over 60%, lacked a TATA box, and contained several sequences matching transcription factor binding sites, including nine SP-1 sites, one AP-1 site, and three CACC boxes. The promoter activity of a 475-bp fragment from within this region was demonstrated by chloramphenicol acyltransferase assays. Northern blotting revealed variable expression of the human AC RNA; i.e., expression of the major 2.4-kb transcript was high in heart and kidney, followed by lung and placenta, but low in pancreas, liver, brain, and skeletal muscle. Two minor AC transcripts of 1.7 and 1.2 kb also were detected in heart and skeletal muscle. The human AC **gene** was mapped to the chromosomal region 8p21.3-p22 by in situ hybridization and FISH analyses, syntenic with the mouse chromosomal location. Finally, three new missense mutations, E138V, R254G, and P362R, were identified in the human AC **gene** from FD patients. Mutant AC **cDNAs** containing these point mutations were constructed and examined using the FLAG-tagged expression system. Although the levels of protein expression for these mutant ACs were about equivalent to that of the controls, their enzymatic activity was markedly reduced, confirming their authenticity.

L25 ANSWER 17 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:793628 SCISEARCH
THE GENUINE ARTICLE: 245YZ
TITLE: Regulation of cytochrome P450 expression by sphingolipids
AUTHOR: Merrill A H (Reprint); NikolovaKarakashian M; Schmelz E M; Morgan E T; Stewart J
CORPORATE SOURCE: EMORY UNIV, SCH MED, DEPT BIOCHEM, ROLLINS RES CTR 4113, ATLANTA, GA 30322 (Reprint); EMORY UNIV, DEPT PHARMACOL, ATLANTA, GA 30322; CLARK ATLANTA UNIV, DEPT BIOL SCI, ATLANTA, GA 30314
COUNTRY OF AUTHOR: USA
SOURCE: CHEMISTRY AND PHYSICS OF LIPIDS, (NOV 1999) Vol. 102, No. 1-2, pp. 131-139.
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND.
ISSN: 0009-3084.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 37

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Sphingolipids modulate many aspects of cell function, including the expression of cytochrome P450, a superfamily of heme proteins that participate in the oxidation of a wide range of compounds of both endogenous (steroid hormones and other lipids) and exogenous (e.g. alcohol, drugs and environmental pollutants) origin. Cytochrome P450-2C11 (CYP 2C11) is down-regulated in response to interleukin-1 beta (IL-1 beta), and this response involves the hydrolysis of sphingomyelin to ceramide as well as ceramide to sphingosine, and phosphorylation of sphingosine to sphingosine 1-phosphate. Activation of **ceramidase** (s) are a key determinant of which bioactive sphingolipid metabolites are formed in response to IL-1 beta. **Ceramidase** activation also appears to account for the loss of expression of CYP 2C11 when hepatocytes

are placed in cell culture, and the restoration of expression when they are plated on Matrigel; hence, this pathway is influenced by, and may mediate, interactions between hepatocytes and the extracellular matrix. Recent studies using inhibitors of sphingolipid metabolism have discovered that sphingolipids are also required for the induction of CYP 1A1 by 3-methylcholanthrene, however, in this case, the requirement is for de novo sphingolipid biosynthesis rather than the turnover of complex sphingolipids. These findings illustrate how changes in sphingolipid metabolism can influence the regulation of at least several isoforms of cytochrome P450. (C) 1999 Elsevier Science Ireland Ltd. All rights reserved.

L25 ANSWER 18 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:499583 SCISEARCH
THE GENUINE ARTICLE: 209DP
TITLE: Yeast sphingolipids - Structure, biological importance and metabolism
AUTHOR: Bauman M (Reprint); Mesaric M; Maric L
CORPORATE SOURCE: UNIV ZAGREB, SCH MED, DEPT CHEM & BIOCHEM, SALATA 3, HR-10000 ZAGREB, CROATIA (Reprint); UNIV ZAGREB, FAC FOOD SCI & BIOTECHNOL, DEPT BIOCHEM ENGN, ZAGREB 10000, CROATIA
COUNTRY OF AUTHOR: CROATIA
SOURCE: FOOD TECHNOLOGY AND BIOTECHNOLOGY, (APR-JUN 1999) Vol. 37, No. 2, pp. 127-137.
Publisher: FACULTY FOOD TECHNOLOGY BIOTECHNOLOGY, UNIV ZAGREB, KACIECEVA 23, 41000 ZAGREB, CROATIA.
ISSN: 1330-9862.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: AGRI
LANGUAGE: English
REFERENCE COUNT: 68

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Sphingolipids, detected and named by J. L. W. Thudicum more than a hundred years ago, have a common long chain sphingoid base. In most mammals this base is sphingosine. In yeasts, phytosphingosine occurs. Complex sphingolipids are made of sphingoid base to which a fatty acid is linked via an amide bond. Yeast sphingolipids are involved in membrane signaling, regulation of cell wall biosynthesis, phospholipid biosynthesis and binding of cell surface glycoproteins. Besides, they are proven to play important roles in signal transduction during the heat stress response, regulation of calcium homeostasis or components in calcium-mediated signaling pathways and in regulation of the cell cycle.

The key reaction in yeasts sphingolipids biosynthesis is condensation of palmitoyl-CoA with serine yielding D-3-ketosphinganine. This reaction is catalyzed by serine palmitoyltransferase; the mechanism by which yeast cells regulate activity of the enzyme and the concentration of sphingolipids is still being investigated. Little is known about sphingolipids breakdown pathways in yeasts. A form of mammalian sphingomyelinase was found to exist in Saccharomyces cerevisiae. There are no data on the activity of **ceramidase** in the yeast. Secretory pathway is regarded the main pathway of sphingolipid transport in the cell; Golgi appears to be the branching point in this process.

L25 ANSWER 19 OF 46 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1999091888 MEDLINE
DOCUMENT NUMBER: 99091888 PubMed ID: 9874672
TITLE: **Ceramidase** activity in bacterial skin flora as a possible cause of ceramide deficiency in atopic dermatitis.
AUTHOR: Ohnishi Y; Okino N; Ito M; Imayama S
CORPORATE SOURCE: Department of Dermatology, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
SOURCE: CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, (1999 Jan) 6 (1) 101-4.
Journal code: 9421292. ISSN: 1071-412X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316

Entered Medline: 19990301

AB A marked decrease in the content of ceramide has been reported in the horny layer of the epidermis in atopic dermatitis (AD). This decrease impairs the permeability barrier of the epidermis, resulting in the characteristic dry and easily antigen-permeable skin of AD, since ceramide serves as the major water-holding molecule in the extracellular space of the horny layer. On the other hand, the skin of such patients is frequently colonized by bacteria, most typically by Staphylococcus aureus, possessing **genes** such as those for sphingomyelinase, which are related to sphingolipid metabolism. We therefore tried to identify a possible correlation between the ceramide content and the bacterial flora obtained from the skin of 25 patients with AD versus that of 24 healthy subjects, using a thin-layer chromatographic assay of the sphingomyelin-associated enzyme activities secreted from the bacteria. The findings of the assay demonstrated that **ceramidase**, which breaks ceramide down into sphingosine and fatty acid, was secreted significantly more from the bacterial flora obtained from both the lesional and the nonlesional skin of patients with AD than from the skin of healthy subjects; sphingomyelinase, which breaks sphingomyelin down into ceramide and phosphorylcholine, was secreted from the bacterial flora obtained from all types of skin at similar levels for the patients with AD and the healthy controls. The finding that the skin of patients with AD is colonized by **ceramidase**-secreting bacteria thus suggests that microorganisms are related to the deficiency of ceramide in the horny layer of the epidermis, which increases the hypersensitivity of skin in AD patients by impairing the permeability barrier.

L25 ANSWER 20 OF 46 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 1999240501 MEDLINE
DOCUMENT NUMBER: 99240501 PubMed ID: 10222235
TITLE: Nitric oxide stimulates chronic ceramide formation in glomerular endothelial cells.
AUTHOR: Huwiler A; Dorsch S; Briner V A; van den Bosch H; Pfeilschifter J
CORPORATE SOURCE: Zentrum der Pharmakologie, Klinikum der Johann Wolfgang Goethe-Universitat, Theodor-Stern-Kai 7, Frankfurt am Main, D-60590, Germany.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 Apr 29) 258 (1) 60-5.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990527

AB Exposure of glomerular endothelial cells for 24 h to compounds releasing NO, including spermine-NO, MAHMA-NO, and S-nitroso-glutathione, results in a dose-dependent and delayed (after 24 h) increase in the lipid signaling molecule ceramide. This NO-induced stimulation occurs in a cGMP-independent fashion since the membrane-permeant cGMP analogue dibutyryl cGMP has no effect on chronic ceramide production. Short-term incubation of endothelial cells for 20 min reveals that NO and dibutyryl cGMP fail to stimulate an acute ceramide increase, whereas TNF-alpha, a well-known activator of sphingomyelinases, is able to acutely increase ceramide formation. Interestingly, N-oleoylethanolamine, an acidic **ceramidase** inhibitor, potentiates NO-induced chronic ceramide production, indicating that ceramide generation rather than ceramide metabolism is modulated by NO. Furthermore, NO-induced delayed ceramide formation is partially inhibited by the thiol-specific inhibitor iodoacetamide and the radical scavenger alpha-tocopherol, suggesting a regulatory role of thiol-containing enzymes and the involvement of a redox-sensitive mechanism. In addition, NO causes an increased **DNA** fragmentation in glomerular endothelial cells which is further enhanced by N-oleoylethanolamine and can be mimicked by exogenous ceramide. In summary, these results imply that ceramide represents an important mediator of NO-triggered chronic cell responses like apoptosis. Inhibition of ceramide synthesis may provide a new therapeutic approach to the treatment of pathological conditions involving increased NO formation.

L25 ANSWER 21 OF 46 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 1999351564 MEDLINE
DOCUMENT NUMBER: 99351564 PubMed ID: 10424278
TITLE: A possible role of nuclear ceramide and sphingosine in hepatocyte apoptosis in rat liver.
COMMENT: Comment in: J Hepatol. 1999 Jul;31(1):161-4
AUTHOR: Tsugane K; Tamiya-Koizumi K; Nagino M; Nimura Y; Yoshida S
CORPORATE SOURCE: First Department of Surgery, Research Institute for Disease Mechanism and Control, Nagoya University School of Medicine, Japan.
SOURCE: JOURNAL OF HEPATOLOGY, (1999 Jul) 31 (1) 8-17.
Journal code: 8503886. ISSN: 0168-8278.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990921
Last Updated on STN: 19990921
Entered Medline: 19990907

AB BACKGROUND/AIMS: Portal vein branch ligation induces apoptosis of hepatocytes in the ligated lobes in rat liver. Sphingomyelin degradation was studied during the process to evaluate its possible involvement in apoptosis in vivo. METHODS: **DNA** scissions were detected by the terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) and an agarose gel electrophoresis of **DNA**. Using both ligated and non-ligated lobes, we measured activities of sphingomyelin degradation enzymes and contents of their products in purified nuclei and plasma membrane. RESULTS: **DNA** fragmentation was detectable in the ligated lobes at 90 min after the portal vein branch ligation by gel electrophoresis. At 15 h after the ligation, 27% of hepatocytes became TUNEL-positive. Prior to the onset of apoptosis, the activity of neutral sphingomyelinase increased in the nuclei of hepatocytes in ligated lobes (30 min after the ligation). The increase in sphingomyelinase paralleled its reaction product, ceramide. This was followed by the elevation of **ceramidase** activity in nuclei (60 min after the ligation) in association with an increase of its reaction product, sphingosine. Activities of these two enzymes and their products increased for at least 90 min. These changes were not observed in nuclei of the non-ligated lobes, or in the plasma membranes from either ligated or non-ligated lobes. CONCLUSIONS: These results, specific to the liver where apoptosis is being generated, suggest that nuclear sphingomyelin breakdown with an accumulation of ceramide and/or sphingosine in nuclei may induce the apoptosis of hepatocytes in vivo.

L25 ANSWER 22 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:331060 BIOSIS
DOCUMENT NUMBER: PREV199800331060
TITLE: Mechanisms of apoptosis in oligodendrocytes.
AUTHOR(S): Scurlock, B. [Reprint author]; Dawson, G.
CORPORATE SOURCE: Dep. Pediatr.; Committee Neurobiol., Univ. Chicago, Chicago, IL 60637, USA
SOURCE: FASEB Journal, (April 24, 1998) Vol. 12, No. 8, pp. A1341. print.
Meeting Info.: Meeting of the American Society for Biochemistry and Molecular Biology. Washington, D.C., USA. May 16-20, 1998. American Society for Biochemistry and Molecular Biology.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1998
Last Updated on STN: 12 Aug 1998

L25 ANSWER 23 OF 46 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 1998198396 MEDLINE
DOCUMENT NUMBER: 98198396 PubMed ID: 9531498
TITLE: Metabolism and apoptotic properties of elevated ceramide in

HT29rev cells.
AUTHOR: Veldman R J; Klappe K; Hoekstra D; Kok J W
CORPORATE SOURCE: Department of Physiological Chemistry, University of Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen, The Netherlands.
SOURCE: BIOCHEMICAL JOURNAL, (1998 Apr 15) 331 (Pt 2) 563-9.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 19980716
Entered Medline: 19980706

AB Ceramide (Cer) has been implicated in the regulation of apoptosis. In this study, we elevated cellular Cer levels in human colon-carcinoma (HT29(rev)) cells by incubating the cells in the presence of bacterial sphingomyelinase (bSMase) or, alternatively, in the presence of C2-Cer, a short-chain analogue of the sphingolipid. bSMase treatment did not induce apoptosis in these cells, as revealed by a lack of both **DNA** fragmentation and cleavage of poly(ADP-ribose)polymerase. In contrast, apoptosis did occur upon addition of C2-Cer. These findings led us to study whether differences in the metabolic fate of the excess of Cer, as generated by both treatments, contributed to the observed difference in apoptosis-inducing capacity. C2-Cer was rapidly taken up by HT29(rev) cells and accumulated due to the absence of substantial metabolic conversion. Upon addition of bSMase, hydrolysis of sphingomyelin resulted in a reduction of that pool to 20% compared with control values, accompanied by a multi-fold increase in Cer level. In spite of the continuous presence of active bSMase, the Cer increase turned out to be transient. Cer levels reached their maximum 1-2 h after addition of bSMase, followed by a significant decrease. Excessive Cer was mainly turned over via cerebrosides into complex glycolipids, including gangliosides. In the presence of glucosylceramide synthase- and/or **ceramidase** inhibitors, this conversion was significantly blocked and bSMase-generated Cer accumulated in the cells. However, even under these conditions apoptosis did not occur. In conclusion, the inability of bSMase to induce apoptosis of HT29(rev) cells does not appear to be due to rapid metabolic conversion of excessive Cer. Since apoptosis is induced upon addition of C2-Cer, we therefore propose that the intracellular target involved in the propagation of the apoptotic signal is reached by C2-Cer, but not by bSMase-generated Cer.

L25 ANSWER 24 OF 46 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 1998317541 MEDLINE
DOCUMENT NUMBER: 98317541 PubMed ID: 9653654
TITLE: Cloning and characterization of the full-length **cDNA** and genomic sequences encoding murine acid **ceramidase**.
AUTHOR: Li C M; Hong S B; Kopal G; He X; Linke T; Hou W S; Koch J; Gatt S; Sandhoff K; Schuchman E H
CORPORATE SOURCE: Department of Human Genetics, Mount Sinai School of Medicine, New York, New York 10029, USA.
CONTRACT NUMBER: HD 28607 (NICHD)
SOURCE: GENOMICS, (1998 Jun 1) 50 (2) 267-74.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF157500
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981008
Last Updated on STN: 20000303
Entered Medline: 19981001

AB The full-length **cDNA** and genomic sequences encoding murine acid **ceramidase** (AC; E.C. 3.5.1.23) have been isolated and characterized. The 2176-bp **cDNA** was approximately 80% identical to the human **cDNA** (Koch et al., 1996) and predicted a 394-amino-acid polypeptide that was approximately 90% identical to the

human protein. A fluorescence-based assay system was developed to determine AC enzymatic activity, and transfection of COS-1 cells with the full-length mouse **cDNA** led to increased AC activity, demonstrating its functionality. The murine AC **gene**, which spanned approximately 38 kb, consisted of 14 exons separated by 13 introns. The exons ranged in size from 46 to 1038 bp and were flanked by exon/intron junctions that adhered closely to known donor and acceptor splice site consensus sequences. Exon 1 encoded the putative translation start site and the signal peptide region, while exon 14 encoded the carboxy end of the AC polypeptide and all of the 3' untranslated region. Sequence analysis of a 497-bp region upstream from the first in-frame ATG revealed several features of a housekeeping promoter, as well as several tissue-specific and/or hormone-inducible regulatory sites. Insertion of this sequence into a chloramphenicol acyltransferase (CAT) expression vector led an approximately fivefold increase in CAT activity after transfection into NIH3T3 cells. Northern blot analysis and enzymatic assays also were carried out on various murine tissues to examine AC expression. Of the tissues studied, the highest AC activity and mRNA levels were found in the kidney, followed by the brain; almost no AC activity or mRNA was found in the testis or skeletal muscle. These latter studies provided clear evidence that despite the housekeeping function of AC, its expression was tissue-specific.

L25 ANSWER 25 OF 46 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 1998082818 MEDLINE
DOCUMENT NUMBER: 98082818 PubMed ID: 9422355
TITLE: Programmed cell death in cortical chick embryo astrocytes is associated with activation of protein kinase PK60 and ceramide formation.
AUTHOR: Mangoura D; Dawson G
CORPORATE SOURCE: Department of Pediatrics, University of Chicago Medical School, Illinois 60637, USA.
CONTRACT NUMBER: HD-09402 (NICHD)
NS-36866 (NINDS)
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1998 Jan) 70 (1) 130-8.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 20020420
Entered Medline: 19980202

AB Embryonic astrocytes respond readily to serine/threonine kinase regulation in terms of cytoskeleton assembly, mitotic activity, and cell fate. We now present evidence that these responses include apoptosis. Staurosporine induced apoptosis in astrocyte cultures derived from chick embryo cerebral hemispheres, as assayed both by immunocytochemical detection of new 3-hydroxy **DNA** ends and production of 200-bp **DNA** fragment laddering. Staurosporine treatment also resulted in the prolonged (>24 h) activation of a 60-kDa serine/threonine protein kinase (PK60), increased ceramide formation (fourfold after 24 h), increased glutamine synthetase activity, and significant apoptosis (40%) after 24 h. PK60 was shown to be cytoskeleton associated and its activity, as measured by phosphorylation of myelin basic protein, was rapid, increased for up to 3 h, and was stable for at least 24 h. Other protein kinase C inhibitors, H8, sphingosine, calphostin C, or the protein kinase A inhibitor KT5720 did not induce either PK60 activation or apoptosis. The dose-dependent increase in [3H]palmitate labeling of ceramide and a specific decrease in labeling of its precursor sphingomyelin were not blocked by the biosynthetic inhibitor fumonisin betal but were increased (in a dose-dependent manner) by the coaddition of the **ceramidase** inhibitor oleoylethanolamine. Exogenous addition of C2-ceramide induced apoptosis but did not activate PK60. These results suggest that apoptosis in embryonic astrocytes involves pathways similar to those described in other cell types and that the activation of PK60 and formation of ceramide are early events in the pathway.

L25 ANSWER 26 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1998:243038 SCISEARCH

THE GENUINE ARTICLE: ZC371
TITLE: Roles of sphingosine-1-phosphate in cell growth, differentiation, and death
AUTHOR: Spiegel S (Reprint); Cuvillier O; Edsall L; Kohama T; Menzeleev R; Olivera A; Thomas D; Tu Z; VanBrocklyn J; Wang F
CORPORATE SOURCE: GEORGETOWN UNIV, MED CTR, DEPT BIOCHEM & MOL BIOL, 357 BASIC SCI BLDG, 3900 RESERVOIR RD NW, WASHINGTON, DC 20007 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: BIOCHEMISTRY-MOSCOW, (JAN 1998) Vol. 63, No. 1, pp. 69-73. Publisher: PLENUM PUBL CORP, CONSULTANTS BUREAU, 233 SPRING ST, NEW YORK, NY 10013. ISSN: 0006-2979.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Recent evidence suggests that branching pathways of sphingolipid metabolism may mediate either apoptotic or mitogenic responses depending on the cell type and the nature of the stimulus. While ceramide has been shown to be an important regulatory component of apoptosis induced by tumor necrosis factor a and the Fas ligand, sphingosine-1-phosphate (SPP), a further metabolite of ceramide, has been implicated as a second messenger in cellular proliferation and survival induced by platelet-derived growth factor, neuronal growth factor, and serum. SPP protects cells from apoptosis resulting from elevations of ceramide. Inflammatory cytokines stimulate sphingomyelinase, but not **ceramidase**, leading to accumulation of ceramide, whereas growth signals also stimulate **ceramidase** and sphingosine kinase leading to increased SPP levels. We propose that the dynamic balance between levels of sphingolipid metabolites, ceramide, and SPP and consequent regulation of different members of the mitogen-activated protein kinases (JNK versus ERK) family is an important factor that determines whether a cell survives or dies.

L25 ANSWER 27 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1998:577328 SCISEARCH
THE GENUINE ARTICLE: BL26E
TITLE: Sphingosine-1-phosphate in cell growth and cell death
AUTHOR: Spiegel S (Reprint); Cuvillier O; Edsall L C; Kohama T; Menzeleev R; Olah Z; Olivera A; Pirianov G; Thomas D M; Tu Z X; VanBrocklyn J R; Wang F
CORPORATE SOURCE: GEORGETOWN UNIV, MED CTR, DEPT BIOCHEM & MOL BIOL, 353 BASIC SCI BLDG, 3900 RESERVOIR RD NW, WASHINGTON, DC 20007 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (JUN 1998) Vol. 845, pp. 11-18. Publisher: NEW YORK ACAD SCIENCES, 2 EAST 63RD ST, NEW YORK, NY 10021. ISSN: 0077-8923.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 52

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Recent evidence suggests that branching pathways of sphingolipid metabolism may mediate either apoptotic or mitogenic responses depending on the cell type and the nature of the stimulus. While ceramide has been shown to be an important regulatory component of apoptosis induced by tumor necrosis factor alpha and Pas ligand, sphingosine-1-phosphate (SPP), a further metabolite of ceramide, has been implicated as a second messenger in cellular proliferation and survival induced by platelet-derived growth factor, nerve growth factor, and serum. SPP protects cells from apoptosis resulting from elevations of ceramide. Inflammatory cytokines stimulate sphingomyelinase, but not **ceramidase**, leading to accumulation of ceramide, whereas growth signals also stimulate **ceramidase** and sphingosine kinase leading to increased SPP levels. We propose that the dynamic balance between

levels of sphingolipid metabolites, ceramide, and SPP, and consequent regulation of different family members of mitogen-activated protein kinases (JNK versus ERK), is an important factor that determines whether a cell survives or dies.

L25 ANSWER 28 OF 46 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 97373568 MEDLINE
DOCUMENT NUMBER: 97373568 PubMed ID: 9228043
TITLE: Bimodal regulation of **ceramidase** by interleukin-1beta. Implications for the regulation of cytochrome p450 2C11.
AUTHOR: Nikolova-Karakashian M; Morgan E T; Alexander C; Liotta D C; Merrill A H Jr
CORPORATE SOURCE: Department of Biochemistry, Emory University, Atlanta, Georgia 30322-3050, USA.
CONTRACT NUMBER: GM 46368 (NIGMS)
GM 46897 (NIGMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jul 25) 272 (30) 18718-24.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19980206
Entered Medline: 19970909

AB Interleukin 1beta (IL-1beta) induces the hydrolysis of sphingomyelin (SM) to ceramide (Cer) in primary cultures of rat hepatocytes, and Cer has been proposed to play a role in the down-regulation of cytochrome P450 2C11 (CYP2C11) and induction of alphal-acid glycoprotein (AGP) by this cytokine (Chen, J., Nikolova-Karakashian, M., Merrill, A. H. & Morgan, E. T. (1995) J. Biol. Chem. 270, 25233-25238). Nonetheless, some of the features of the down-regulation of CYP2C11 do not fit a simple model of Cer as a second messenger as follows: N-acetylsphinganine (C2-DHCer) is as potent as N-acetylsphingosine (C2-Cer) in suppression of CYP2C11; the IL-1beta concentration dependence for SM turnover is different from that for the increase in Cer; and the increase in Cer mass is not equivalent to the amount of SM hydrolyzed nor the time course of SM hydrolysis. In this article, we report that these discrepancies are due to activation of **ceramidase** by the low concentrations of IL-1beta (approximately 2.5 ng/ml) that maximally down-regulate CYP2C11 expression, whereas higher IL-1beta concentrations (that induce AGP) do not activate **ceramidase** and allow Cer accumulation. This bimodal concentration dependence is demonstrated both by in vitro **ceramidase** assays and in intact hepatocytes using a fluorescence Cer analog, 6-((N-(7-nitrobenz-2-oxa-1, 3-diazol-4-yl)amino)-Cer (NBD-Cer), and following release of the NBD-fatty acid. IL-1beta increases both acid and neutral **ceramidase** activities, which appear to be regulated by tyrosine phosphorylation because pretreatment of hepatocytes with sodium vanadate increases (and 25 microM genistein reduces) the basal and IL-1beta-stimulated **ceramidase** activities. Since these findings suggested that sphingosine (and, possibly, subsequent metabolites) is the primary mediator of the down-regulation of CYP2C11 by IL-1beta, the effects of exogenous sphingosine and C2-Cer on expression of this **gene** were compared. Sphingosine was more potent than C2-Cer in down-regulation of CYP2C11 when added alone or with fumonisin B1 to block acylation of the exogenous sphingosine. Furthermore, the suppression of CYP2C11 by C2-Cer (and C2-DHCer) is probably mediated by free sphingoid bases, rather than the short chain Cer directly, because both are hydrolyzed by hepatocytes and increase cellular levels of sphingosine and sphinganine. From these observations we conclude that sphingosine, possibly via sphingosine 1-phosphate, is a mediator of the regulation of CYP2C11 by IL-1beta in rat hepatocytes and that **ceramidase** activation provides a "switch" that determines which sphingolipids are elevated by this cytokine to produce multiple intracellular responses.

L25 ANSWER 29 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:206812 CAPLUS
DOCUMENT NUMBER: 126:304005

TITLE: Human lactase-phlorizin hydrolase expressed in COS-1 cells is proteolytically processed by the lysosomal pathway
AUTHOR(S): Wuethrich, Marcel; Sterchi, Erwin E.
CORPORATE SOURCE: Institute of Biochemistry and Molecular Biology and Department of Paediatrics, University of Berne, Bern, 3012, Switz.
SOURCE: FEBS Letters (1997), 405(3), 321-327
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lactase-phlorizin hydrolase (LPH) (EC 3.2.1.23/62), a major glycoprotein of the microvillus membrane of human small intestinal epithelial cells (enterocytes), is vital for the digestion of lactose during early infancy. The enzyme is synthesized in enterocytes as a single-chain precursor and subsequently proteolytically processed to the mature microvillus membrane-bound form. Because it has been reported that COS-1 cells were not able to proteolytically process LPH to the mature protein, these cells have been used as a model system to study potential roles of different proteases. COS-1 cells transfected with a full-length **cDNA** for human LPH synthesized enzymically active enzyme. Immunopptn. of the expressed glycoproteins and their subsequent anal. by SDS-PAGE showed synthesis of two polypeptide species having apparent mol. masses of 210 and 220 kDa, resp., corresponding to the high-mannose (pro-LPHh) form and the complex glycosylated (pro-LPHc) form of the LPH precursor. Surprisingly, an addnl. polypeptide species corresponding in size to the mature LPH found in human intestinal cells was also detected after longer chase periods. The source of this species was clearly pro-LPH, as its formation was inhibited by Brefeldin A. The cleaved form of LPH was not found on the cell surface; furthermore, its formation was prevented by an inhibitor of lysosomal function. It is concluded that in transfected COS-1 cells pro-LPH is transported to the cell surface, from which it is internalized and enters the lysosomal pathway, where proteolytic cleavage leads to a mol. not unlike mature LPH.

L25 ANSWER 30 OF 46 MEDLINE on STN
ACCESSION NUMBER: 97427910 MEDLINE
DOCUMENT NUMBER: 97427910 PubMed ID: 9284098
TITLE: Decreased level of prosaposin in atopic skin.
AUTHOR: Cui C Y; Kusuda S; Seguchi T; Takahashi M; Aisu K; Tezuka T
CORPORATE SOURCE: Department of Dermatology, Kinki University School of Medicine, Osaka, Japan.
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1997 Sep) 109 (3) 319-23.
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 20000303
Entered Medline: 19970924

AB In the skin of atopic dermatitis patients, the amount of ceramides in the stratum corneum is decreased. Although the cause of this decrease may be due to the higher activity of acylase, a decrease in the activity of sphingolipid activator proteins may also be the cause. A polyclonal antibody to saposin D, elicited by immunizing rabbits with the synthetic polypeptide from **cDNA** of saposin D, cross-reacted with a single 65-kDa epidermal protein of pI 5.6 in a 2-dimensional immunoblot study, suggesting that it was prosaposin, the precursor protein of saposin D, from its molecular weight and demonstrating its immunohistochemical localization in the innermost cell layers of the stratum corneum of the skin. The antigenic material was also observed in the epithelium of the esophagus, pneumocytes of the lungs, hepatocytes, and glandular cells of the stomach. Immunoelectron microscopy showed the antigenic material in the cytoplasm of the granular cells and the intercellular spaces, either between the stratum granulosum and the stratum corneum or on the stratum corneum cell envelope. By ELISA, the amount of the 65-kDa protein in the inner surface skin of the upper arm of atopic dermatitis patients

(nonlesional skin) [4.1 +/- 2.0 microg per 7 mm2 (mean +/- SD), n = 10] was found to be significantly decreased ($p < 0.05$) to 66% of that in the normal control (6.2 +/- 1.5 microg per 7 mm2, n = 10). Therefore, the suppression of prosaposin synthesis may be related to the abnormal stratum corneum formation in atopic skin through lower activation of glucosylcerebrosidase or sphingomyelinase.

L25 ANSWER 31 OF 46 MEDLINE on STN
ACCESSION NUMBER: 97160772 MEDLINE
DOCUMENT NUMBER: 97160772 PubMed ID: 9007051
TITLE: Sphingolipids--the enigmatic lipid class: biochemistry, physiology, and pathophysiology.
AUTHOR: Merrill A H Jr; Schmelz E M; Dillehay D L; Spiegel S; Shayman J A; Schroeder J J; Riley R T; Voss K A; Wang E
CORPORATE SOURCE: Department of Biochemistry, Emory University School of Medicine, Atlanta, Georgia 30322-3050, USA.
CONTRACT NUMBER: 1RO1 GM43880 (NIGMS)
CA61774 (NCI)
DK41487 (NIDDK)
+
SOURCE: TOXICOLOGY AND APPLIED PHARMACOLOGY, (1997 Jan) 142 (1) 208-25. Ref: 168
Journal code: 0416575. ISSN: 0041-008X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970224

AB The "sphingosin" backbone of sphingolipids was so named by J. L. W. Thudichum in 1884 for its enigmatic ("Sphinx-like") properties. Although still an elusive class of lipids, research on the involvement of sphingolipids in the signal transduction pathways that mediate cell growth, differentiation, multiple cell functions, and cell death has been rapidly expanding our understanding of these compounds. In addition to the newly discovered role of ceramide as an intracellular second messenger for tumor necrosis factor-alpha, IL-1beta, and other cytokines, sphingosine, sphingosine-1-phosphate, and other sphingolipid metabolites have recently been demonstrated to modulate cellular calcium homeostasis and cell proliferation. Perturbation of sphingolipid metabolism using synthetic and naturally occurring inhibitors of key enzymes of the biosynthetic pathways is aiding the characterization of these processes; for examples, inhibition of cerebroside synthase has indicated a role for ceramide in cellular stress responses including heat shock, and inhibition of ceramide synthase (by fumonisins) has revealed the role of disruption of sphingolipid metabolism in several animal diseases. Fumonisins are currently the focus of a FDA long-term tumor study. This review summarizes recent research on (i) the role of sphingolipids as important components of the diet, (ii) the role of sphingoid base metabolites and the ceramide cycle in expression of **genes** regulating cell growth, differentiation, and apoptosis, (iii) the use of cerebroside synthase inhibitors as tools for understanding the role of sphingolipids as mediators of cell cycle progression, renal disease, and stress responses, and (iv) the involvement of disrupted sphingolipid metabolism in animal disease and cellular deregulation associated with exposure to inhibitors of ceramide synthase and serine palmitoyltransferase, key enzymes in de novo sphingolipid biosynthesis. These findings illustrate how an understanding of the function of sphingolipids can help solve questions in toxicology and this is undoubtedly only the beginning of this story.

L25 ANSWER 32 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:379677 CAPLUS
DOCUMENT NUMBER: 125:41763
TITLE: Site-specific biomolecular complexes for drug delivery to brain
INVENTOR(S): Katz, Robert; Tomoaia-Cotisel, Maria

PATENT ASSIGNEE(S): Molecular/structural Biotechnologies, Inc., USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604001	A1	19960215	WO 1995-US9870	19950804
W: AU, CA, HU, JP, NO				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5716614	A	19980210	US 1994-286327	19940805
US 6005004	A	19991221	US 1995-487693	19950607
AU 9532755	A1	19960304	AU 1995-32755	19950804
EP 952841	A1	19991103	EP 1995-929378	19950804
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				

PRIORITY APPLN. INFO.: US 1994-286327 19940805
US 1995-487693 19950607
WO 1995-US9870 19950804

AB The title complexes comprise a therapeutic, prophylactic, or diagnostic agent (biol. active mol.) and an .omega.-3 fatty acid (esp. .alpha.-linolenic, eicosapentaenoic, or docosahexaenoic acid) or deriv. thereof. The complexes are further covalently bonded with cationic carriers and permeabilizer peptides for delivery across the blood-brain barrier and with targeting moieties for uptake by target brain cells. The complexes are particularly useful for delivery of a biol. active agent to the glial tissue of the brain as well as to the cortical cholinergic and adrenergic neurons. Thus, acid .beta.-glucosidase (glucocerebrosidase) may be conjugated with a polylysine carrier to which are also attached docosahexaenoyl residues, a directing moiety such as tetanus toxin fragment C or NGF, and cationized human albumin to facilitate penetration of the blood-brain barrier for enzyme replacement therapy in Gaucher's disease (no data).

L25 ANSWER 33 OF 46 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 97115857 MEDLINE
DOCUMENT NUMBER: 97115857 PubMed ID: 8955159
TITLE: Molecular cloning and characterization of a full-length complementary **DNA** encoding human acid **ceramidase**. Identification Of the first molecular lesion causing Farber disease.
AUTHOR: Koch J; Gartner S; Li C M; Quintern L E; Bernardo K; Levran O; Schnabel D; Desnick R J; Schuchman E H; Sandhoff K
CORPORATE SOURCE: Institut fur Organische Chemie und Biochemie, D-53121 Bonn, Federal Republic of Germany.
CONTRACT NUMBER: HD 28607 (NICHD)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 20) 271 (51) 33110-5.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U70063
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 20000407
Entered Medline: 19970123

AB Human acid **ceramidase** ((AC) N-acylsphingosine amidohydrolase, EC 3.5. 1.23) hydrolyzes the sphingolipid ceramide into sphingosine and free fatty acid. Ceramide is an essential component of all sphingolipids and an important cell-signaling molecule. Moreover, an inherited deficiency of AC activity leads to the lysosomal storage disorder known as Farber disease. Human AC was purified from urine, and 117 amino acid residues were determined by microsequencing. Degenerative oligonucleotide probes were then constructed and used to screen for human fibroblast and pituitary **cDNA** libraries. Several partial **cDNA** clones were obtained, and two of these were combined to construct a full-length **cDNA** containing a 17-base pair (bp) 5'-untranslated sequence, a

1185-bp open reading frame encoding 395 amino acids, a 1110-bp 3'-untranslated sequence, and an 18-bp poly(A) tail. Transient expression of the full-length **cDNA** in COS-1 cells led to a 10-fold increase in AC activity. In addition, biosynthetic studies carried out in the transfected cells demonstrated that 13-kDa (alpha) and 40-kDa (beta) AC subunits were derived from a common 55-kDa precursor encoded by the full-length **cDNA**. This protein pattern was identical to that seen in normal human skin fibroblasts. A homoallelic point mutation (T222K) was also identified in the AC **gene** of a patient suffering from Farber disease, further confirming the authenticity of the full-length **cDNA**.

L25 ANSWER 34 OF 46 EMBASE
on STN
ACCESSION NUMBER: 97035288 EMBASE
DOCUMENT NUMBER: 1997035288
TITLE: In situ assay of acid sphingomyelinase and **ceramidase** based on LDL- mediated lysosomal targeting of ceramide-labeled sphingomyelin.
AUTHOR: Levade T.; Leruth M.; Graber D.; Moisand A.; Vermeersch S.; Salvayre R.; Courtoy P.J.
CORPORATE SOURCE: T. Levade, Laboratoire de Biochemie, CJF INSERM 9206, Institut Louis Bugnard, 31403 Toulouse Cedex 4, France
SOURCE: Journal of Lipid Research, (1996) 37/12 (2525-2538).
Refs: 65
ISSN: 0022-2275 CODEN: JLPRAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The activity of lysosomal sphingolipid hydrolases is usually estimated in vitro from complex assays on cell lysates under artificial conditions including the presence of detergents and substrate analogs. However, the measure of their effective activity in situ (i.e., in living cells) is necessary to understand the normal intracellular sphingolipid turnover. Moreover, their determination in cells from patients with genetic enzyme deficiencies represents a key parameter of the pathophysiology of sphingolipid storage disorders. In this report, we have developed a procedure for estimating the effective activity of lysosomal sphingomyelinase and **ceramidase** in situ. This procedure is based on the selective targeting to lysosomes of a natural substrate under physiological conditions of substrate influx. Epstein-Barr virus-transformed human lymphoid cells and human skin fibroblasts were incubated with purified human low density lipoprotein (LDL) containing [3H]ceramide-labeled sphingomyelin. Data demonstrate that this substrate is internalized through the apolipoprotein B/E receptor pathway and targeted to lysosomes. Lysosomal localization of the incorporated substrate was evidenced by ultrastructural autoradiography and subcellular, fractionation as well as by metabolic studies in mutant cells. Short-term pulse-chase experiments with LDL-associated [3H]ceramide-labeled sphingomyelin allowed us to determine the effective activity of lysosomal sphingomyelinase and **ceramidase** in normal cells. Initial velocities of sphingomyelin and ceramide degradation were, respectively, estimated at 0.66 and 1.14 nmol .cntdot. h-1 mg cell protein-1 in lymphoid cells, and 5.4 and 3 nmol .cntdot. h-1 cell protein-1 in skin fibroblasts. The advantages and applications of these in situ studies are discussed.

L25 ANSWER 35 OF 46 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 96192128 MEDLINE
DOCUMENT NUMBER: 96192128 PubMed ID: 8627293
TITLE: Staurosporine induces programmed cell death in embryonic neurons and activation of the ceramide pathway.
AUTHOR: Wiesner D A; Dawson G
CORPORATE SOURCE: Department of Pediatrics, University of Chicago, Illinois, USA.
CONTRACT NUMBER: HD-06426 (NICHD)
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1996 Apr) 66 (4) 1418-25.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960708
Last Updated on STN: 19960708
Entered Medline: 19960625

AB We activated the death pathway in embryonic chick cerebral hemisphere neuron (E7CH) cultures with staurosporine (0.1-1.0 microM) and observed the meporphological changes, **DNA** laddering patterns, and **DNA** fragmentation (determined by Hoechst 33258 dye) associated with apoptosis. N-Acylsphingosine (C2-ceramide), a soluble ceramide analogue, was also able to induce apoptosis in these cells with the same characteristics and in the same time frame. We then observed that staurosporine was effective in inducing hydrolysis of sphingomyelin to ceramide as measured by a threefold increase in ceramide mass and increased incorporation of [3H]-palmitate into ceramide, concurrent with activating the cell death program. Furthermore, the coaddition of a specific **ceramidase** inhibitor, oleoylethanolamine (15 microM), enhanced the formation of ceramide as well as the degree of **DNA** fragmentation and cell death. Exogenous addition of sphingomyelinase activated the death pathway whereas ceramide glycanase did not, and inhibitors of sphingomyelin or protein synthesis failed to block this type of killing. Our data suggest that formation of ceramide from sphingomyelin is a key event in staurosporine-induced and potentially all programmed cell death.

L25 ANSWER 36 OF 46 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 96346043 MEDLINE
DOCUMENT NUMBER: 96346043 PubMed ID: 8741291
TITLE: Sphingomyelin and its catabolism in cell nucleus: their possible roles in regulation mechanism of **DNA** replication.
AUTHOR: Tamiya-Koizumi K
CORPORATE SOURCE: Laboratory of Cancer Cell Biology, Nagoya University School of Medicine, Aichi.
SOURCE: SEIKAGAKU. JOURNAL OF JAPANESE BIOCHEMICAL SOCIETY, (1996 Jun) 68 (6) 453-63. Ref: 30
Journal code: 0413564. ISSN: 0037-1017.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961204

L25 ANSWER 37 OF 46 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 96:634315 SCISEARCH
THE GENUINE ARTICLE: VD344
TITLE: ACTIVATION OF PHOSPHOLIPASE-D IN HUMAN FIBROBLASTS BY CERAMIDE AND SPHINGOSINE - EVALUATION OF THEIR MODULATORY ROLE IN BRADYKININ STIMULATION OF PHOSPHOLIPASE-D
AUTHOR: MEACCI E; VASTA V; NERI S; FARNARARO M; BRUNI P (Reprint)
CORPORATE SOURCE: UNIV FLORENCE, DEPT BIOCHEM SCI, VIALE GB MORGAGNI 50, I-50134 FLORENCE, ITALY (Reprint); UNIV FLORENCE, DEPT BIOCHEM SCI, I-50134 FLORENCE, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (14 AUG 1996) Vol. 225, No. 2, pp. 392-399.
ISSN: 0006-291X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 28
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the present study tile modulatory action of exogenous short-chain ceramide and sphingosine on phospholipase D (PLD) activity in young and

old human fibroblasts was examined. Sphingosine and also ceramide, thus far described as a negative modulator of PLD, were able to activate PLD. The stimulatory action of the exogenous lipid molecules was mimicked by cell treatment with S.aureus sphingomyelinase (SMase). Similar response was elicited by the sphingoid molecules in young and old cells. Altered levels of sphingosine and ceramide were detected in old fibroblasts confirming that a defect in sphingolipid metabolism occurs in cellular senescence. The modulatory role of sphingoid molecules on the action of bradykinin (BK) in PLD activation was then evaluated in young and old fibroblasts. C-6-ceramide or SMase treatment did nor affect the action of BK on PLD either in young or in old cells, whereas sphingosine further increased PLD activity stimulated by BK in young but not in old cells. In addition, preincubation with N-oleoylethanolamine, a specific inhibitor of **ceramidase**, did not affect BK action on PLD in young fibroblasts but significantly decreased the effect of the peptide in old fibroblasts. These results suggest that a specific alteration of BK segnalatory pathway occurs in old fibroblasts, likely involving sphingosine formation which may account for the potentiated PLD activity induced by the peptide in these cells. (C) 1996 Academic Press, Inc.

L25 ANSWER 38 OF 46 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 96301666 MEDLINE
DOCUMENT NUMBER: 96301666 PubMed ID: 8737258
TITLE: Programmed cell death in neurotumour cells involves the generation of ceramide.
AUTHOR: Wiesner D A; Dawson G
CORPORATE SOURCE: Department of Pediatrics, University of Chicago School of Medicine, IL 60637, USA.
CONTRACT NUMBER: HD-06426 (NICHD)
SOURCE: GLYCOCONJUGATE JOURNAL, (1996 Apr) 13 (2) 327-33.
Journal code: 8603310. ISSN: 0282-0080.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961025
Last Updated on STN: 19980206
Entered Medline: 19961016

AB Ceramide has been typically thought of as the membrane anchor for the carbohydrate in glycosphingolipids but many studies have suggested that it may cause apoptosis. Apoptosis or programmed cell death (PCD) is thought to be responsible for the death of one-half of neurons surviving the development of the nervous system. The potential involvement of the sphingomyelin-ceramide signaling process as an integral part of PCD was therefore examined in several neurotumour cell lines. We show that synthetic C2-ceramide (N-acetylsphingosine), a soluble ceramide analogue, can rapidly trigger PCD in these cells, characterized by: 1) classic **DNA** laddering on agarose gels; 2) **DNA** fragmentation as determined by Hoechst Dye; and 3) cell viability (mitochondrial function and intact nuclei) assays. We report that staurosporine can both activate PCD (by all three criteria above) in neurotumour cells and increase both the formation of ceramide and ceramide mass. Both ceramide formation and the induction of PCD were further enhanced by the co-addition of a **ceramidase** inhibitor oleoylethanolamine (25 microM). Staurosporine and oleoylethanolamine were similarly effective in inducing ceramide formation and PCD in immortalized hippocampal neurons (HN-2) and immortalized dorsal root ganglion cells (F-11). Our data suggests that formation of ceramide is a key event in the induction of PCD in neuronally derived neurotumour cells.

L25 ANSWER 39 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:182114 BIOSIS
DOCUMENT NUMBER: PREV199698738243
TITLE: A simple method for screening for farber disease on cultured skin fibroblasts.
AUTHOR(S): Chatelut, Martine; Feunteun, Jean; Harzer, Klaus; Fensom, Anthony H.; Basile, Jean-Pierre; Salvayre, Robert; Levade, Thierry [Reprint author]
CORPORATE SOURCE: Lab. de Biochimie Maladies Metab., CJF INSERM 9206, Inst. Louis Bugnard, Bat. L3, C.H.U. Rangueil, 1 Avenue Jean

Poulhes, 31054 Toulouse Cedex, France
SOURCE: Clinica Chimica Acta, (1996) Vol. 245, No. 1, pp. 61-71.
CODEN: CCATAR. ISSN: 0009-8981.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Apr 1996
Last Updated on STN: 10 Jun 1996

AB Farber disease is an inborn lysosomal storage disorder characterized by accumulation of ceramide in the patient's tissues due to the deficient activity of acid **ceramidase**. Currently, confirmation of the diagnosis is performed in an extremely limited number of laboratories. We therefore developed a procedure which does not require any particular sphingolipid substrate and is based on the quantitation of ceramide levels in cultured skin fibroblasts. In the method we devised, the ceramide present in cellular lipid extracts subjected to mild alkaline hydrolysis was quantified using the commercially available diacylglycerol kinase kit. We show that both primary cultures of skin fibroblasts and SV40-transformed fibroblasts derived from a series of patients with Farber disease exhibit ceramide excess as compared to their normal counterparts (2345-17 153 pmol/mg cell protein in Farber cells vs. 432-1298 pmol/mg cell protein in controls). Use of this simple method should greatly facilitate the biochemical diagnosis of Farber disease.

L25 ANSWER 40 OF 46 EMBASE
on STN
ACCESSION NUMBER: 95307269 EMBASE
DOCUMENT NUMBER: 1995307269
TITLE: Differential regulation of sphingomyelinase and **ceramidase** activities by growth factors and cytokines. Implications for cellular proliferation and differentiation.
AUTHOR: Coroneos E.; Martinez M.; McKenna S.; Kester M.
CORPORATE SOURCE: Department of Medicine, School of Medicine, Case Western Reserve University,Cleveland, OH 44106, United States
SOURCE: Journal of Biological Chemistry, (1995) 270/40 (23305-23309).
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Sphingosine is a product of sphingolipid metabolism that has been linked to a protein kinase C-independent mitogenic response. In previously published data, utilizing an in vitro model system for platelet-derived growth factor (PDGF)-induced vascular smooth muscle proliferation, we have demonstrated that sphingosine is increased at the expense of a concomitant decrease in ceramide formation, implicating an altered **ceramidase** activity. To explore mechanisms of growth factor-stimulated sphingosine formation, we have developed and investigated a cell-free model system assessing **ceramidase** activity. We now report that an alkaline, membrane-associated, **ceramidase** activity in the rat glomerular mesangial cell, a smooth muscle-like pericyte, is up.regulated by growth factors, apparently via a tyrosine kinase phosphorylation mechanism. PDGF also stimulated sphingomyelinase activity which generates sufficient substrate to drive the subsequent **ceramidase** reaction. Inflammatory cytokines, including interleukin-1, and tumor necrosis factor-.alpha., stimulated sphingomyelinase but not **ceramidase** activity, a result consistent with the cellular accumulation of the ceramide, apoptidic, differentiating second messenger. Mitogenic vasoconstrictor peptides such as endothelin-1 stimulated neither sphingomyelinase nor **ceramidase** activities. An inhibitor of **ceramidase** activity, N-oleoylethanolamine, reduced PDGF- but not endothelin-1-stimulated proliferation. Thus, we conclude that, in mesangial cells, growth factors but not vasoconstrictor peptides or cytokines induce mitogenesis, in part, through **ceramidase** -mediated sphingosine formation.

L25 ANSWER 41 OF 46 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 95136252 MEDLINE
DOCUMENT NUMBER: 95136252 PubMed ID: 7834642

TITLE: Induction of apoptosis by sphingosine in human leukemic HL-60 cells: a possible endogenous modulator of apoptotic **DNA** fragmentation occurring during phorbol ester-induced differentiation.
AUTHOR: Ohta H; Sweeney E A; Masamune A; Yatomi Y; Hakomori S; Igarashi Y
CORPORATE SOURCE: Biomembrane Institute, Seattle, Washington 98119.
CONTRACT NUMBER: CA42505 (NCI)
SOURCE: CANCER RESEARCH, (1995 Feb 1) 55 (3) 691-7.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19970203
Entered Medline: 19950228

AB The present studies were undertaken to characterize the potential role of sphingosine in the regulation of apoptosis in HL-60 promyelocytic leukemia cells. A 6-h exposure of HL-60 cells to sphingosine or its methylated derivative, N,N-dimethylsphingosine, caused internucleosomal **DNA** fragmentation and stereotypical morphological changes characteristic of apoptosis (i.e., cell shrinkage, nuclear condensation, and the formation of apoptotic bodies), as well as that to pharmacological inhibitors of protein kinase C such as 1-(5-isoquinolinesulfonyl)-2-methylpiperazine and staurosporine. Apoptosis by sphingosine and N,N-dimethylsphingosine was measured using a flow cytometric method. The percentages of apoptotic cells in cultures treated with sphingosine (10 microM) and N,N-dimethylsphingosine (10 microM) for 6 h were 55.6 +/- 7.8% and 84.2 +/- 11.6%, respectively. HL-60 cells were induced to differentiate toward macrophages by treatment with 5 nM 4 beta-phorbol 12-myristate 13-acetate (PMA). Internucleosomal **DNA** fragmentation, which was a hallmark of apoptosis, was first detected after 10-h exposure to PMA and increased with longer treatment. Sphingosine concentrations in the cells increased concomitantly with the increasing proportion of apoptotic cells during cell differentiation. Sphingosine level in HL-60 cells differentiated by treatment with PMA for 48 h was about 3.3-fold greater than that in untreated cells. Differentiated HL-60 cells exhibited a markedly increased conversion of exogenously added [3H]ceramide to [3H]sphingosine, indicating elevation of **ceramidase** activity. Moreover, exposure to sphingosine resulted in down-regulation of c-myc mRNA. These observations suggest the possible role of sphingosine in induction of apoptotic **DNA** fragmentation during PMA-induced differentiation in myeloid leukemia cells. Sphingosine may function as an endogenous modulator mediating the apoptotic signal.

L25 ANSWER 42 OF 46 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 96017933 MEDLINE
DOCUMENT NUMBER: 96017933 PubMed ID: 7588966
TITLE: A family with combined Farber and Sandhoff, isolated Sandhoff and isolated fetal Farber disease: postnatal exclusion and prenatal diagnosis of Farber disease using lipid loading tests on intact cultured cells.
AUTHOR: Levade T; Enders H; Schliephacke M; Harzer K
CORPORATE SOURCE: Laboratoire de Biochimie, CJF INSERM 9206, Institut Louis Bugnard, CHU Rangueil, Toulouse, France.
SOURCE: EUROPEAN JOURNAL OF PEDIATRICS, (1995 Aug) 154 (8) 643-8.
Journal code: 7603873. ISSN: 0340-6199.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 20000407
Entered Medline: 19951215

AB An earlier described patient with combined sphingolipidoses, Farber and Sandhoff disease, had two healthy older brothers and two further sibs, one with Sandhoff disease and one (a fetus) with Farber disease, showing segregation of the respective **genes**. The prenatal diagnosis in

the latter was performed using lipid (sphingomyelin and glucosylceramide) loading tests on the cultured amniotic fluid cells. After 1-3 days of incubation the cells' lipid extract revealed radioactive ceramide to be released and highly accumulated. The deficiency in acid **ceramidase** was known from the patient with the combined diseases. Confirmation of the prenatal Farber diagnosis was done by similar loading tests on the fetal fibroblasts and by analysis of liver lipids of the less than 18-week-old fetus. CONCLUSION: This is the first report on the use of lipid loading tests on intact cultured cells for prenatal diagnosis of Farber disease. The postnatal diagnosis of Farber disease can also be readily made using those tests, as was shown in four further cases.

L25 ANSWER 43 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:140992 CAPLUS
DOCUMENT NUMBER: 122:25203
TITLE: The cis-element CE-LPH1 of the rat intestinal lactase **gene** promoter interacts in vitro with several nuclear factors present in endodermal tissues
AUTHOR(S): Boukamel, Rita; Freund, Jean-Noeel
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Unite 381, 3 avenue Moliere, Strasbourg, 67200, Fr.
SOURCE: FEBS Letters (1994), 353(1), 108-12
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have shown by electrophoretic mobility shift assays that the nucleotide sequence CE-LPH1, centered at position -49 with respect to the transcription start site of the rat **gene** encoding intestinal lactase-phlorizin hydrolase, interacts in vitro with nuclear proteins present in the jejunum of suckling animals. Proteins binding to this element were also found in organs of endodermal origin that do not (or no longer) express lactase-phlorizin hydrolase, i.e. the colon, lung and the liver, but not in the brain. However, a **DNA**-protein interaction was hardly detected with nuclear exts. prepd. from adult tissues, although typical factors binding to the Sp1 binding site were detected at the adult stage as in the sucklings. Southwestern blotting expts. conducted with nuclear exts. prepd. from the tissues of suckling rats indicated that CE-LPH1 interacts with several factors in the jejunum, colon, lung and the liver. Some of these **DNA**-binding proteins are specifically expressed in the jejunum or in the liver, whereas others seem to be shared with the colon and the lung. Hence, the cis-element CE-LPH1 located in close vicinity to the pseudo-TATA-box of the intestinal lactase-phlorizin hydrolase **gene** promoter interacts in vitro with a family of nuclear proteins which may represent markers of the endodermal lineage predominantly expressed prior to weaning.

L25 ANSWER 44 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1988:506693 CAPLUS
DOCUMENT NUMBER: 109:106693
TITLE: The precursor of sulfatide activator protein is processed to three different proteins
AUTHOR(S): Fuerst, Werner; Machleidt, Werner; Sandhoff, Konrad
CORPORATE SOURCE: Inst. Org. Chem. Biochem., Univ. Bonn, Bonn, D-5300/1, Fed. Rep. Ger.
SOURCE: Biological Chemistry Hoppe-Seyler (1988), 369(5), 317-28
CODEN: BCHSEI; ISSN: 0177-3593
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A protein, called component C, which seems to be related to sulfatide activator and to a recently described activator of glucosylceramidase (A1 activator) (Kleinschmidt, T., et al., 1987) was purified and sequenced. It consists of 78 amino acids and carries 1 carbohydrate chain at asparagine-20. Component C shows 21.5% sequence homol. to sulfatide activator and 34.2% homol. to A1 activator. The **cDNA** sequence of the sulfatide activator precursor (Dewji, N. N., et al., 1987) was aligned with the protein sequences of sulfatide activator, A1 activator, and component C. After minor corrections of the **DNA** sequence it seems 3 different proteins are derived from the sulfatide activator

precursor by proteolytic processing. Possible processing sites were on the precursor at sites adjacent to the N-termini and C-termini of the mature proteins. Data on the processing of sulfatide activator (Fujibayashi, S.; Wenger, D. A., 1986) support that processing occurs by simultaneous cleavage at all possible sites.

L25 ANSWER 45 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1984:24775 BIOSIS
DOCUMENT NUMBER: PREV198426024775; BR26:24775
TITLE: GLUCOSYL **CERAMIDASE** DEFICIENCY IN EPSTEIN BARR VIRUS LYMPHOID CELL LINES FROM GAUCHER PATIENTS USING NATURAL SUBSTRATES.
AUTHOR(S): MARET A [Reprint author]; SALVAYRE R; NEGRE A; LENOIR G; VUILLAUME M; DOUSTE-BLAZY L
CORPORATE SOURCE: INSERM U 101, BIOCHIM DES LIPIDES, LAB BIOCHIM MED, FAC MED, PURPAN 37, ALLEES JULES GUESDE, 31000 TOULOUSE, FR
SOURCE: IRCS (International Research Communications System) Medical Science Library Compendium, (1983) Vol. 11, No. 3, pp. 214-215.
DOCUMENT TYPE: Article
FILE SEGMENT: BR
LANGUAGE: ENGLISH

L25 ANSWER 46 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1984:15363 BIOSIS
DOCUMENT NUMBER: PREV198426015363; BR26:15363
TITLE: PHENOTYPIC ALTERATION ACCOMPANIES CHANGES IN GLYCO SPHINGO LIPID BIOSYNTHESIS IN 3T3-KIMSV CELLS INDUCED BY ALPHA FLUORO PALMITIC-ACID.
AUTHOR(S): SOLTYSIAK R M [Reprint author]; MATSUURA F; SWEELEY C C
CORPORATE SOURCE: BIOCHEM DEP, UNIV MICH STATE UNIV, EAST LANSING, MICH 48824, USA
SOURCE: Federation Proceedings, (1983) Vol. 42, No. 7, pp. ABSTRACT 1535.
Meeting Info.: 74TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, SAN FRANCISCO, CALIF., USA, JUNE 5-9, 1983. FED PROC.
CODEN: FEPRA7. ISSN: 0014-9446.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH

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